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ORIGINAL ARTICLE

Differential effects of gastric bypass and banding on the cardiovascular risk profile in morbidly obese subjects: The correlation with plasma apolipoprotein A-IV concentration

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Abstract *Background:* Weight loss (5–10%) improves obesity-associated cardiovascular risk factors. The aim of this work was to study the effect of 2 commonly performed bariatric surgical procedures; laparoscopic Roux-en-Y gastric bypass (RYGBP) and laparoscopic gastric band (BAND), on the cardiovascular risk profile in morbidly obese patients and its correlation with the plasma apolipoprotein (apo) A-IV level.

Patient and method: This study was carried prospectively on 34 patients scheduled for bariatric surgery. They were randomly assigned into two groups; group 1 = BAND (18 cases), group 2 = gastric bypass RYGBP (16 cases). Both groups were studied preoperatively and twelve months after surgery. Data collected included changes of body mass index (BMI), blood pressure, fasting blood sugar, fasting serum insulin, insulin resistance (HOMA-IR) and lipid profile. In addition, apo A-IV was determined by the Western blot technique.

Results: The results demonstrated a highly significant reduction in body weight as determined by reduction in the BMI in both groups I & II compared to preoperative measurements. Moreover, both groups had a significantly lower systolic blood pressure, fasting blood glucose (FBG), fasting serum insulin and HOMA-IR twelve months after operation. The changes in BMI, systolic blood pressure; FBG and HOMA-IR were significantly more in group II than in group I. The lipid profiles in group I & II before surgery were similar. The HDL-cholesterol was significantly higher in both

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groups I & II 12 months after surgery. In addition, apo A-IV levels increased after surgery in both groups.
Conclusion: Both gastric band and gastric bypass are associated with significant improvement of the cardiovascular risk profile, although it is more pronounced after gastric bypass. The improvement correlates well with the increase of apo A-IV in both groups.
Thus Apo A-IV may play a positive role in improving the cardiovascular risk profile after bariatric surgery.

1. Introduction

Overweight and obesity are rapidly growing to an epidemic proportion all over the world. Severe obesity (BMI $\geqslant 40$ Kg/m^2) is associated with significant medical co-morbidities as well as reduced life expectancy. Health service use and medical costs associated with obesity related diseases have increased dramatically in the last years.[1] Obesity may affect the heart through its influence on known risk factors such as dyslipidemia, hypertension, impaired glucose tolerance, inflammatory markers, obstructive sleep apnea/hypoventilation, and the prothrombotic state. It is well known that weight reduction improves obesity-related cardiovascular risk factors.[2] The use of conventional weight-loss diets and drug therapy has been shown to decrease the risk for conversion from impaired glucose tolerance to overt diabetes and can maintain blood pressure reductions over prolonged periods of follow-up. However, they may be associated with toxic effect, also they are usually ineffective for severe obesity, and bariatric surgery has been proposed as an alternative therapy.[3] More dramatic weight loss after bariatric surgery has been associated with even greater health benefits, especially patients with diabetes[4] (Figs. 1 and 2).

Apolipoproteins, are the protein components of lipoprotein particles, they play an active role in the lipid metabolism. In addition to the well-known apolipoproteins, apo A-IV apolipoprotein is a 46-KD glycoprotein. It is synthesized by the small intestine in response to lipid absorption and the formation of chylomicrons.[5] The majority of apo A-IV in the circulation exists as free protein while the remainder is associated with circulating HDL. It is also produced in the hypothalamic arcuate nucleus. Despite its responsiveness to lipid intake, the exact function for apo A-IV has not yet been widely recognized. It has been proposed to play many functions in vivo including: food intake regulation, demonstrating it to be a satiety factor[6,7] gastrointestinal motility, structural constituent of lipoproteins, protection against lipid oxidation and atherosclerosis, recently identified as an anti-inflammatory protein and can also mimic many of the roles of apo A-I in terms of lipid binding and cholesterol efflux.[8]

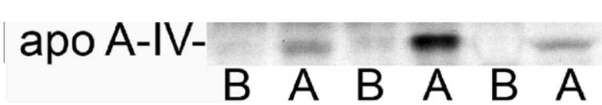

Figure 1 Shows changes in apo A-IV after surgery as determined by the western blotting technique and detected by densitometry. The Apo A-IV was significantly increased after surgery in both groups, however, the increase (estimated in arbitrary values) was significantly greater in group II (Table 3).

2. Aim of the work

The aim of this work was to study the effect of 2 commonly performed bariatric surgical procedures; laparoscopic Roux-en-Y gastric bypass (RYGBP) and laparoscopic gastric band

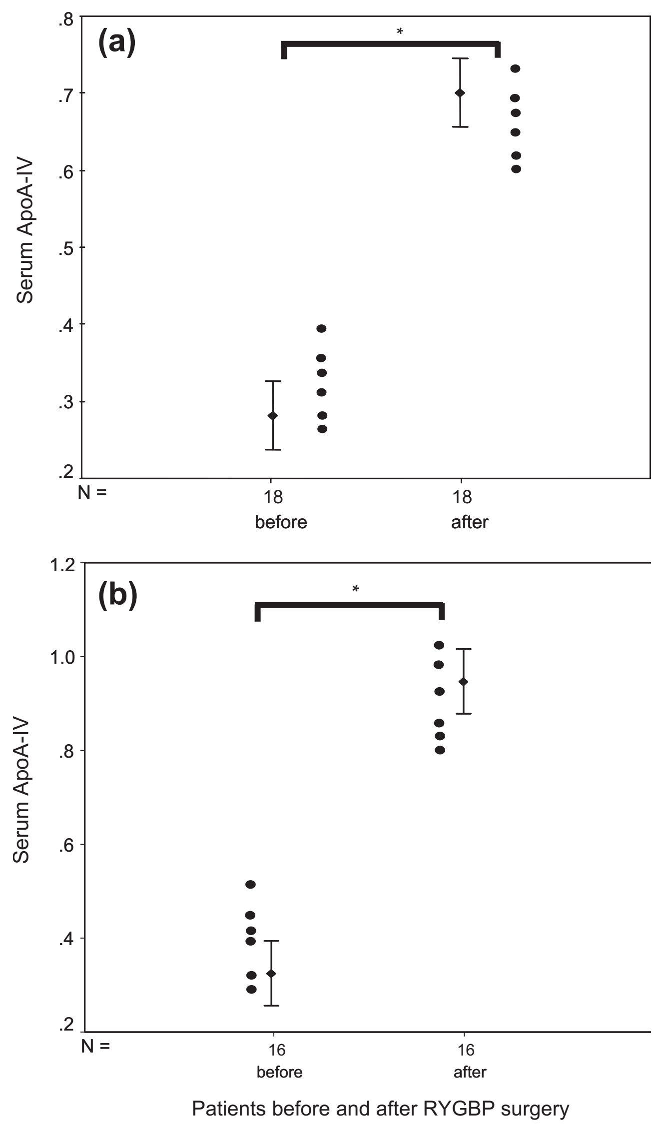

Figure 2 (a) Serum apo A-IV densitometric changes (vertical axis) before and after BAND procedure. (b) Serum apo A-IV densitometric changes (vertical axis) before and after RYGBP procedure.

(BAND), on the cardiovascular risk profile in morbidly obese patients and its correlation with apo A-IV level.

3. Patients and methods

This prospective study was conducted in the Department of Surgery at Alexandria Main University Hospital during the period from 2008 through 2010. The study was approved by the Ethics Committee of the Faculty of Medicine of the University of Alexandria (Alexandria, Egypt). An informed consent was obtained from all patients included in the study. Forty patients were considered for surgery based upon satisfaction of the minimal criteria for bariatric surgical treatment, as determined by the Consensus Development Panel of the National Institutes of Health.[9] In brief, surgery may be considered in those persons with body mass index (BMI) greater than 40 kg/m^2, or greater than 35 kg/m^2, when there are co-morbidities which are life-threatening or detrimental to activities of daily living. Patients were randomly assigned by using sealed-envelope technique to either laparoscopic gastric band (BAND) as group I or laparoscopic Roux-en-Y gastric bypass (RYGBP) as group II.

3.1. Surgical procedures

The surgical procedure for the BAND consisted of placement of the Swedish adjustable gastric band (Obtech® and Ethicon Endo-Surgery®) around the proximal stomach. We used the pars flaccida technique. A retrogastric tunnel was created above the peritoneal reflection of the bursa omentalis. The band was then passed through this tunnel and locked. The anterior wall of the stomach below the band is then secured to the wall above the band with interrupted non absorbable gastro-gastric sutures to avoid slippage. The band placed around the upper stomach creates a small pouch with a narrowed outlet. The inner surface of the band is inflatable and connected by kink-resistant tubing to the access port. The port was placed subcutaneously permitting postoperative percutaneous stoma size adjustment. The first filling of the gastric band was performed 4 to 6 weeks postoperatively.

The surgical procedure for RYGBP consisted of creation of a 15- to 30-mL pouch that was isolated from the distal stomach by several applications of a linear stapler. The jejunum is divided 50 cm distal to the ligament of Treitz, and the distal limb is connected to the gastric pouch (antecolic-antegastric), using a linear cutter, creating an alimentary Roux limb. The proximal bowel segment (biliopancreatic limb) is connected to the alimentary limb through a jejunojejunostomy 100 to 150 cm distal to the gastrojejunostomy. For patients whose BMI was less than 50, a 100-cm Roux limb was measured; for those whose BMI was greater than 50, we used a 150-cm limb.[11]

Before surgery and 12 months after, blood samples were taken after overnight fast of at least 12 h, and patients were weighed in a light gown. Blood samples were used for determination of lipid profile, glucose and insulin as well as Western blot (WB) assay to detect apo A-IV. In all pre-menopausal women, lipids were studied within the first 5 days of the menstrual cycle to avoid hormonal interference that may modify lipid pattern. Other collected data included systolic and diastolic blood pressure.

Table 1 Demographic data of the study population.

	Group I (BAND) $n = 18$	Group II (RYGBP) $n = 16$	*P*-value
Age (years)	37 ± 6	39 ± 4.5	0.38
Sex (M/F)	3/15	2/16	0.67
BMI (kg/m^2)	45.8 ± 2.7	46.2 ± 2.56	0.336
Body weight (kg)	138.7 ± 22.98	142.7 ± 22.6	0.221

Fasting plasma glucose (FBG) was measured by the hexokinase method and plasma insulin was determined using an IMMULITE 2500 autoanalyzer (Siemens Medical Diagnostics) in an immunometric chemiluminescent test with two binding sites (noncompetitive) on solid phase. The homeostasis model of assessment of insulin resistance (HOMA-IR) was then calculated by the following formula: fasting serum insulin concentration (mIU/mL) × blood glucose concentration (mmol/L)/22.5.[12]

Total cholesterol, HDL-cholesterol and triglycerides were measured enzymatically using commercial kits. The apolipoprotein B100 was measured using enzyme linked immunoassays. LDL cholesterol was calculated using Friedwald's formula, since no subject had triglycerides □350 mg/dl.[9]

Blood samples for apo A-IV estimation were collected in EDTA vacutainers, centrifuged at low speed (3000 rpm) and serum was frozen at −80 °C until assayed. Apo A-IV level was estimated using the western blot technique.

3.2. Apo A-IV assay using the western blot technique

A single gel was run for each patient and loaded with 2 samples; one before and the second after surgery. Western blot (WB) assays to detect apo A-IV were run using 10% sodium dodecyl sulfate gel electrophoresis and transferred to Immobilon membranes of Millipore®. IgG anti-human apo A-IV was used as the primary antibody at 1/500 dilution (with blocking solution). Horseradish peroxidase (HRP)-conjugated pig anti-rabbit IgG at 1/15,000 dilution (with blocking solution) was used as the secondary antibody (Dako, Glostrup, Denmark). Non-specific binding was prevented using a blocking solution (phosphate-buffered saline (PBS) with bovine serum albumin (BSA)) at 2% (w/v, BSA/PBS). WBs were developed using the Super-Signal West Pico Chemiluminescent substrate for HRP detection (Pierce®, Rockford, IL, USA). Relative quantities and optical density were estimated by densitometric scanning (Phoretix 1D gel Analysis Software Non-linear Dynamics, Newcastle, UK).[13]

3.3. Statistical analysis

Data were prospectively collected. All data analyses were performed with the Statistical Package for the Social Sciences version 15 software (SPSS, Inc., Chicago, IL). Results are expressed as mean ± standard deviation. The Student's *t* test and paired t test were used for continuous variables. The chi-squared test was used for category variables. Spearman correlation coefficient was used to detect the correlation between different variables. All P-values were two sided. A value of $P \leqslant 0.05$ was considered statistically significant.

Table 2 Body mass index (BMI), fasting plasma glucose (FPG), fasting insulin and HOMA-IR before and 12 months after surgery.

	Group I (BAND) n = 18			Group II (RYGBP) n = 16			P_2
	Preoperative	12 Months after operation	P	Preoperative	12 Months after operation	P	
BMI	45.8 ± 2.7	37.1 ± 1.6	0.006*	46.2 ± 2.56	32.0 ± 2.8	0.0013*	0.0013*
%Body weight decrease	26.25 ± 22.13			31.5 ± 19.58			0.025
FBG (mg/dl)	108.0 ± 18.4	92.5 ± 12.0	0.033*	111.0 ± 17.46	80.0 ± 8.9	0.012*	0.0358*
Serum insulin (mIU/mL)	22.4 ± 3.65	9.85 ± 0.65	0.001*	23.5 ± 4.01	8.12 ± 0.76	0.0001*	0.042*
HOMA-IR	2.62 ± 0.625	1.75 ± 0.55	0.0158*	2.71 ± 0.71	1.23 ± 0.68	0.011*	0.046*

* Statistically significant result.
P: comparison with the preoperative level within the same group.
P_2: Comparison between the changes in the two groups.

Table 3 Systolic and diastolic blood pressure (BP) in groups I & II; before and 12 months after surgery.

	Group I (BAND) n = 18			Group II (RYGBP) n = 16			P_2
	Preoperative	12 Months	P	Preoperative	12 Months	P	
Systolic BP (mmHg)	146.2 ± 17.82	131.9 ± 10.3	0.001	148.6 ± 18.0	126.7 ± 9.9	0.001	0.003*
Diastolic BP (mmHg)	92.5 ± 10.0	84.5 ± 6.4	0.231	91.5 ± 10.2	81.5 ± 8.8	0.01	0.013*

* Statistically significant result.
P: Comparison with the preoperative level within the same group (paired t test).
P_2: Comparison between the changes in the two groups (student's t test).

Table 4 Plasma lipid profile in groups I & II before and 12 months after surgery.

	Group I (BAND) n = 18			Group II (RYGBP) n = 16			P_2
	Preoperative	12 Months	P	Preoperative	12 Months	P	
Total cholesterol (mg/dl)	247.1 ± 33.8	196.2 ± 23.5	0.001	246.71 ± 33.8	178.8 ± 19.3	0.001	0.001*
HDL Cholesterol (mg/dl)	41.4 ± 7.6	44.5 ± 4.3	0.106	40.8 ± 6.5	47.4 ± 3.5	0.035*	0.106
LDL Cholesterol (mg/dl)	162.4 ± 62.2	110.3 ± 16.8	0.001	160.4 ± 61.28	67.4 ± 23.5	0.001	0.0001*
Triglycerides (mg/dl)	172.0 ± 97.7	143.5 ± 40.1	0.001	169.0 ± 98.1	101.5 ± 23.3	0.001	0.0001*
Apo-B 100 (mg/dl)	112.3 ± 6.9	78.3 ± 6.1	0.001*	109.3 ± 7.7	72.5 ± 7.6	0.001*	0.032*
Apo-B100/LDL-C	0.69 ± 0.233	0.70 ± 0.285	0.26	0.68 ± 0.33	1.09 ± 0.277	0.106	0.098
ApoA-IV(optical density)	0.23 ± 0.08	0.86 ± 0.1	0.001*	0.31 ± 0.09	1.11 ± 0.1	0.001*	0.034*

* Statistically significant result.
P: Comparison with the preoperative level within the same group (paired t test).
P_2: Comparison between the changes in the two groups (student's t test).

4. Results

Out of 40 patients originally randomized to either BAND or RGBP, 34 patients completed the 12 month follow up and constituted the material of this study. They were 18 patients in the BAND group and 16 patients in the RGBP group. The preoperative clinical characteristics of each of the two studied groups are shown in Table 1. There were no significant differences in age, sex, body weight, or BMI between the two surgical groups.

Twelve months after surgery (Table 2), the body mass index (BMI) decreased from 45.8 ± 2.7 and 46.2 ± 2.56 to 37.1 ± 1.6 and 32.0 ± 2.7 in group I (BAND) and group II (RGBP) respectively. This was associated with significant improvement of glucose metabolism parameters in both groups. HOMA-IR decreased from 2.62 ± 0.625 and 2.71 ± 0.71to 1.75 ± 0.55 and 1.23 ± 0.68 in group I and group II, respectively. The changes in BMI, body weight, FBG, fasting insulin, and HOMA-IR were significantly greater in RGBP group compared to those in BAND group (Table 2).

Other cardiovascular risk factors that were determined are shown in Tables 3 and 4. There was a significant reduction of total cholesterol, LDL cholesterol, triglycerides and Apo B 100 after surgery in both groups. On the other hand, the HDL cholesterol increased from 41.4 ± 7.6 mg/dl, 40.8 ± 3.5 preoperatively to 44.5 ± 4.3 and 47.4 ± 3.5 after surgery in groups I & II, respectively. All lipid profile parameters showed a greater change after surgery in group II than in group I (Table 4). Similarly, Apo B 100 level was reduced from 112.3 ± 6.9 mg/dl to 78.3 ± 6.1 mg/dl in group I and from 109.3 ± 7.7 mg/dl to 72.5 ± 7.6 mg/dl in group II after surgery. The decrease in Apo B100 was significantly greater in group II.

There was a statistically significant correlation between the change of the arbitrary value of apo A-IV and those of all measured cardiovascular risk factors after surgery (Table 5).

Table 5 Correlation between apo A-IV change and cardiovascular risk factors changes after surgery (n = 34).

	R	P
Apo A-IV # BMI	0.462	0.0015*
Apo A-IV # systolic B.P.	0.398	0.014*
Apo A-IV # Total cholesterol	0.46	0.0023*
Apo A-IV # HOMA-IR	0.365	0.046*
Apo A-IV # HDL	0.45	0.036*
Apo A-IV # triglycerides	0.39	0.041*

* Statistically significant result.

5. Discussion

The field of bariatric surgery has evolved over the past 50 years; weight loss has almost been over shadowed by the extraordinary effects on obesity related co-morbidities such as hyperlipidemia, hypertension, and diabetes. This type of surgery was known to induce marked weight reduction, and it had a remarkable effect on circulating lipid levels in severely hyperlipidemic patients.[14] In this study we examined the effects of weight loss after bariatric surgery on reductions in cardiovascular risk factors.

In the present study, the cardiovascular risk factors including systolic blood pressure, insulin resistance, lipid profile and BMI were studied before and one year after surgery. Results revealed a significant improvement of the lipids profile, including apo B100 in both groups; group I (BAND) and group II (RYGBP). Improvement involved a significant decrease in total cholesterol, LDL cholesterol and triglycerides. However, the decrease was greater in group II than in group I. The greater reduction in group II than I could be explained by the greater degree of weight loss and lower energy intake following RYGBP. While gastric band (BAND) is a purely restrictive procedure, the mechanism for weight loss after Roux-en-Y gastric bypass include: (i) restriction of food intake by small gastric pouch and narrow gastrojejunostomy; (ii) mild degree of malabsorption caused by intestinal bypass; and (iii) abdominal discomfort caused by ingestion of concentrated sweets. In addition, the surgical disruptions of the various autonomic nerve fibers that innervate the foregut, may also affect both short- and long-term regulation of gastrointestinal hormonal secretion.[15]

Our study was in agreement with other studies, which reported that subjects with hypercholesterolemia at baseline had normal blood cholesterol levels one year after bariatric surgery. This means that there is no need for lipid-lowering medications any more.[11,15,16] There was an additional beneficial effect, in which HDL-cholesterol levels significantly increased in both groups I & II. This was in agreement with other studies which stated that dyslipidemia associated with obesity is characterized by increased fasting triglyceride and decreased HDL-cholesterol concentrations.[10,11,15,17] This improved lipid profile was associated with increased apo A-IV in both groups, with more significant increase in group II.

The increased apo A-IV observed in our study may be due to recovery of intestinal function, which supports the concept, that plasma apo A-IV is synthesized exclusively by the intestines as mentioned before. Moreover, in a previous study by Tso et al.[7], they stated that chronic consumption of a high-fat diet significantly elevates plasma apo A-IV levels. This elevation is observed during the first week of high fat consumption but disappears during the second week; this proves that auto-regulation of intestinal apo A-IV production in response to diets high in fat. Thus obese persons become less responsive to fat after chronic high-fat diet consumption.

Insulin resistance, in morbidly obese patients is associated with alteration of lipid metabolism, which may be due to associated decreased activity of lipoprotein lipase and increased production of small dense LDL. Insulin resistance also results in elevated free fatty acids secondary to hydrolysis of stored triglycerides in adipose tissues.[16–21] Weight loss improves insulin sensitivity proved by HOMA-IR as we also observed in our patients after surgery. Meneghini[22] suggested that laparoscopic RYGBP has a beneficial effect on glucose metabolism and serum lipid composition in obese type 2 diabetes mellitus (T2DM) patients. They reported that sustained weight loss was associated with maintenance of euglycemia in postoperative obese T2DM patients.

Reversibility of insulin resistance following bariatric surgery is supported by the significant decrease in plasma glucose and improved insulin levels as represented by significant reduction in the HOMA-IR. Previous study reported that in morbidly obese subjects the HOMA-IR reference values considered to represent insulin resistance were around 3.5–3.8.[16] Therefore reduction in HOMA-IR values in this study was to a value of one, suggests that insulin resistance was resolved in both groups. It is well known that stored triglycerides are hydrolyzed to fatty acids and glycerol by the hormone sensitive lipase, whose action is inhibited by insulin.[23] Increased lipolysis, a characteristic of obesity, leads to an increase in circulating free fatty acids FFA, which are transported and oxidized in skeletal muscle. The increased FFA oxidation subsequently leads to inhibition of glucose oxidation. In fact, obese subjects tend to oxidize more lipids than carbohydrates.[24] Also, the detected changes in apolipoproteins in both groups, especially group II following RYGBP resulting in a less atherogenic phenotype may contribute to the improvement in cardiovascular risks which is in agreement with other studies.[21,25,26]

Weight loss of approximately 0.5 kg per week can be achieved by diet alone, and can lead to a decrease in triglycerides, low-density lipoprotein, and total cholesterol. However an overall improvement in the lipid panel; was obtained with a high-dose 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG Co A) inhibitor therapy. In a study performed in patients treated with Cholestagel, a new potent bile acid sequestrant, LDL cholesterol decreased by 19.1%.[27] In addition, Adams et al.[28] stated that weight loss associated with bariatric surgery is more sustainable, and that the improvement in the lipid profile may be superior after surgery.

Fabris et al.[24] have shown that the weight loss after gastric banding produces a decrease in fasting triglyceride levels, an elevation of high-density lipoprotein-cholesterol levels to normal, and improved total cholesterol to high density lipoprotein-cholesterol ratio. Although weight loss associated with bariatric surgery improved dyslipidemia, the changes in the lipid panel appear to be procedure-dependent.[15,16] Meneghini[22] noted 90 percent improvement in cholesterol and triglyceride levels after gastric bypass or biliopancreatic diversion (or duodenal switch) as compared to 50- to 70-percent improvement with gastric banding and gastroplasty. It appears that the malabsorptive aspect of these mixed procedures, in addition to the associated weight loss, plays an important role in improvement of the lipid profile in morbidly obese patients in contrast to weight loss secondary to diet restriction alone.[21] In a Chinese study, results revealed that combination of Chinese medicinal herbs stimulates Apo A-IV promoter activity in gut cells and is associated with reduction of Triglyceride contents in adipocytes and therefore increased apoA-IV level, which may be used to treat obesity.[29]

However, in contrast to our results; Lingenhel et al. studied apo A-IV in obese young adolescents undergoing diet restriction; they concluded that plasma apoA-IV level decreased markedly in overweight adolescents undergoing short-term weight reduction. The decrease is not directly related to the degree of weight loss.[27]

The result of apo A-IV in this study showed a greater increase in group II probably related to the greater degree of weight loss observed after RYGBP as well as regulation of gastrointestinal hormonal secretion such as ghrelin. This result agrees with the results of previous studies.[20,22] Another study reported apo A-IV to be frequently elevated in rodent models of obesity and obese humans.[8] Thus apo A-IV resistance may represent a significant factor known to occur with leptin in obesity, which also regulates apo A-IV secretion.[21,28] It has been demonstrated that intravenous injection of apo A-IV into rats causes a reduction in food intake.[13,22] This observation may be potentially explained by the complex, multi-factorial regulation of food intake.[29]

Plasma lipoproteins, such as high-density lipoprotein (HDL), can serve as carriers for a wide range of proteins that are involved in lipid metabolism, inflammation and atherosclerosis.[9] The identification of HDL-associated proteins is essential with regards to understanding these processes at the molecular level. Therefore, in this study, we performed Western blot analysis to identify apo A-IV associated with human HDL. This technique proved to be a powerful and comprehensive tool for the identification of proteins on HDL.[13]

In this study we did not use ELISA technique, because ELISA works on native protein, while Western works on denatured proteins. Thus ELISA cannot give any information on the purity of the protein. Moreover, cross reactivity of any antibody can't be visualized in ELISA but can be visualized with WB. Therefore, ELISA can sometimes underestimate proteins.[30]

In conclusion, both gastric band and gastric bypass are associated with significant improvement of the cardiovascular risk profile, although it is more pronounced after gastric bypass. The improvement correlates well with increase of apo A-IV in both groups.

Thus, Apo A-IV may play a positive role in improving the cardiovascular risk profile after bariatric surgery and can be a useful tool in clinical monitoring of the patients.

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